RESEARCH ARTICLE

Molecular Docking Study of Substituted Chalcone Compounds as Potential Cyclin-Dependent Protein Kinase 2 (Cdk-2) Inhibitors

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The present investigative studies involve molecular docking study of substituted thiophene-based chalcone compounds (A1-A9) against anti-cancer therapeutic target Cyclin-Dependent Protein Kinase-2 (Cdk-2) (PDB ID: 1HCL) for identifying and developing potential inhibitors. Few imperative physicochemical properties such as Stretching, Bending, Stretching-Bending, Torsion, Non-1,4 VDW, 1,4 VDW, Total Steric Energy for Frame, and Total energy of the best inhibitors have also been determined.

Introduction

The chemistry of chalcone has generated intensive scientific studies throughout the world. Especially interest has been focused on the synthesis and biodynamic activities of chalcone [**1**]. It bears a very good synthons so that variety of novel heterocyclic with good pharmaceutical profile can be designed [**2**]. Chalcone are one of the important secondary metabolite obtained from much edible plant like food, vegetables, tea, spices and natural foodstuffs [**3**]. They are the precursor for the synthesis of many flavonoids and isoflavonoids and also they act as a lead molecule for the synthesis of novel heterocyclic derivative that are used to target the biological structure [**4**]. A wide range of new approaches have been explored by the researchers for synthesis and evaluation of various chalcone and their derivative [**5**]. The potential of chalcone as an excellent pharmacological agent has been identified and the molecule are developed to be used as an antioxidant, antimicrobial, anticancer, anti-inflammatory, etc. [**6**]. It is found in a number of biologically active molecule. In recent time, there has been phenomenol increase in number of publication on versatile chalcone compound which reflect the interest in this field throughout the world [**7**]. Chalcone (1,3-diaryl-2-propene-1-one) which possesses the α,β-unsaturated carbonyl systems, is one of the most ubiquitously found secondary metabolites in the plant kingdom [**8**]. This structure has always been considered has privileged pharmacophore because of its application in synthesis of various five and six membered heterocyclic compound as well as its therapeutic activity against a wide spectrum of diseases and have been reported to possess various biological activities such as antimicrobial, anti-inflammatory, anticancer, antiviral, and antioxidant activities [**9**]. The presence of α, β unsaturated carbonyl system in chalcone make it biologically active [**10**]. The chemistry of chalcones remains a fascination among researcher's in the 21st century due to large number of replaceable hydrogen that allow a large number of derivative and a variety of promising biological activities to be generated; e.g. anti-inflammatory, anti-oxidant, anti-protozoal, anti-obesity, anti-retroviral, etc. [**11**]. They have displaced a broad spectrum of pharmacological activities changes in their structure have offered a high degree of diversity that has proven useful for the development of new medicinal agent having improved potency and lesser toxicity [**12**]. Now days, chalcone is used in a wide range of antimicrobial activities like anti-malarial, anti-tubercular, anti-cancer, anti-diabetic, anti-inflammatory, anti-tumor, anti-viral, anti-bacterial, anti-fungal, anti-oxidant, anti-protozoan, etc [**13**]. It is focus in pharmacological activity. So the chalcones is very important in medical research point of view and its derivatives have many important uses of biological activities [**14**].

The present investigative studies involve molecular docking study of substituted thiophene-based chalcone compounds **(A1-A9)** against anti-cancer therapeutic target Cyclin-Dependent Protein Kinase-2 (Cdk-2) (PDB ID: 1HCL) for identifying and developing potential inhibitors. Few imperative physicochemical properties such as Stretching, Bending, Stretching-Bending, Torsion, Non-1,4 VDW, 1,4 VDW, Total Steric Energy for Frame, and Total energy of the best inhibitors have also been determined.

Experimental

Sketching of ligands

The compounds were primarily drawn in two-dimensional (2D) format by using the ChemDraw® Ultra 8.0 software and then saved as MOL files. The prepared structures were docking by modifying ligand torsion, followed by suitable assignment of protonation states. Several stereochemical structures were created for each ligand at pH target of 7.0±2.0. By utilizing the force field, tautomerized, desalted, and optimized three-dimensional (3D) ligand structures were formed. The dielectric electrostatic constant for the ligands was kept at 1.0 [**15**].

Preparation and validation of protein targets

Target identification is the most fundamental step in a modern drug discovery campaign. The 3D crystal structure of human cyclin dependent kinase-2 (PDB ID: 1HCL) were obtained from protein data bank (PDB). By using the "preprocess and analyze structure", the enzyme targets were prepared by deleting water molecules present in the crystal structures beyond 5A° distance. The proteins were organized by the application of software which assigns the bond order, disulfide bonds, and formal charges to acquire correct geometry. Removal of metal ions, hetero group, and cofactors was carried out. The hydrogen atoms were optimized by keeping all the heavy atoms in place on employing the "impref utility" tool. The hydrogen-bonding network was optimized by making use of "H-bond assignment" tool. The receptor grids were estimated for the proteins so that during the molecular docking, a variety of ligand poses will bind within the predicted active site. The grids were generated at the centroid of the ligand (crystallized with the enzyme) and positioned in such a manner that it would cover the whole ligand (cubic box of specific dimensions). The study was performed by keeping the Van der Waals scale factor at 1.00 and the charge cut off at 0.25 (default parameters). HTVS was carried out and the best scoring ligands subjected to XP docking. The final scoring was done based on the energy-minimized poses and expressed as Glide score. The top scoring ligands were subjected to induced-fit docking (IFD) and the best-docked pose with lowest Glide score value was verified for each ligand [**16**].

Molecular docking studies

When the structure of the target protein is known, structure-based drug design technique can be applied. The free ligands were docked into the active site of the rigid receptor which produces a predicted binding mode and the measure of the quality of the fit of the compound was verified. It has its own significance of ligand binding with the protein in receptor-based computational methods. The affinity between the ligand and macromolecule (receptor) was estimated through molecular docking technique. The IFD also helps in assuming the binding by determining the appropriate interaction with low energy values. The method eliminates the steric clashes and identifies low free energy conformation of each complex. In the IFD technique, the RMSD value cut off of 0.18A° was utilized and Van der Waals scaling was done at 0.7 and 0.5 for receptor and ligand, respectively. The number of poses for each ligand was set at 20 and the side chains were either minimized or eliminated. The procured information exploited to grade the compounds in order to select and experimentally test the subset for biological activity. The Glide score for each ligand was computed [**17**].

Results and discussion

Molecular docking studies

From the *in silico* molecular docking studies of 9 compounds (**A1-A9**), the molecules **A8**, **A4**, **A5**, and **A6** were identified as the best compounds with Dock Score of -11.0653 Kcal/mol (interacts with amino acid residues 85-GLN, 85-LEU), -10.5463 Kcal/mol (interacts with amino acid residue 83-LEU), -10.0299 Kcal/mol (interacts with amino acid residue 145-ASP), and -10.3206 Kcal/mol (interacts with amino acid residues 125-HIS, 145-ASP), respectively (**Table 1**).

Study of best compounds

From the identified best candidates; **A8**, **A4**, **A5**, and **A6**, various physicochemical parameters such as Stretching, Bending, Stretching-Bending, Torsion, Non 1,4 VDW, 1,4 VDW, Total Steric Energy for Frame, and Total energy were calculated (**Table 2**). The results demonstrated that all the compounds were highly stable.

Conclusion

The present *in silico* explorative study represented an enormous effort towards searching few promising thiophene-chalcone low-molecular-weight ligands which could successfully inhibit the most prominent target; Cyclin-Dependent Protein Kinase-2 (Cdk-2) which isgenerally involved in cancer cellproliferation and further metastasis process. These inhibitors may be predicted to play imperative roles in personalized cancer therapies, estrogen receptor–positive breast cancer, HER2-negative breast cancer, lung carcinoma, melanoma, osteosarcoma, ovarian carcinoma, pancreatic carcinoma, sarcomas, chronic lymphocytic leukemia, mantle cell lymphoma, multiple myeloma, non-Hodgkin's lymphoma, metastatic solid tumors, astroglioma, astrocytoma, gliosarcoma, glioblastoma, rectal cancer, hepatocellular carcinoma, thymic carcinoma, malignant thymoma, brain tumors, hematologic malignancies, etc. (**Fig. 1**). The various calculated physicochemical parameters indicated the stability of the identified four best inhibitors. This study will inspire the young researchers and will definitely open new avenues in the primary identification, further development, and final commercialization of the small molecules in chemotherapeutics.

Acknowledgements

No acknowledgements provided.

Conflicts of interest

There are no conflicts to declare.

Keywords

Chalcone, Thiophene, CDK-2, Docking, Inhibitors.

Supporting information

Table 1. Molecular docking studies of various substituted chalcone derivatives.
Table 2. Physicochemical parameters of identified best substituted chalcone candidates.
Figure 1. Specific probable pharmacochemotherapeutics applications of thiophene chalcone-based CDK-2 inhibitors.

References

1. Mahapatra, D.K.; Bharti, S.K.; Asati, V.; *Curr Top Med Chem*., **2017**, *17*, 3146.
2. Mahapatra, D.K.; Bharti, S.K.; Asati, V.; *Eur J. Med Chem*., **2015**, *98*, 69.
3. Mahapatra, D.K.; Bharti, S.K.; Asati, V.; *Eur J. Med Chem*. **2015**, *101*, 496.
4. Mahapatra, D.K., Asati, V., Bharti, S.K.; *Eur J. Med Chem*., **2015**, *92*, 839.
5. Mahapatra, D.K.; Bharti, S.K.; *Life Sci*., **2016**, *148*, 154.
6. Mahapatra, D.K.; Bharti, S.K.; Asati, V.; Singh, S.K.; *Eur J. Med Chem*., **2019**, *174*, 142.
7. Mahapatra, D.K.; Asati, V.; Bharti, S.K.; *Exp Opin Therapeut Pat*. **2019**, *29*, 385.
8. Mahapatra, D.K.; Asati, V.; Bharti, S.K.; *J. Crit Rev*., **2019**, *6*, 1.
9. Mahapatra, D.K.; Shivhare, R.S.; Kumar, P.; *Asian J. Pharm Res*. **2018**, *8*, 6.
10. Mahapatra, D.K., Shivhare, R.S.; Bharti, S.K.; *Res Pharm*., **2017**, *1*, 1.
11. Mahapatra, D.K.; Chhajed, S.S.; Shivhare, R.S.; *Int. J. Pharm Chem Anal*., **2017**, *4*, 30.
12. Mahapatra, D.K.; Shivhare, R.S.; *J. Mod Chem Chem Technol*., **2018**, *9*, 12.
13. Mahapatra, D.K.; Shivhare, R.S.; Asati, V.; *Chron Pharm Sci*., **2018**, *2*, 462.
14. Mahapatra, D.K.; Shivhare, R.S.; Dadure, K.M.; *Acta Scientific Pharm Sci*., **2018**, *2*, 40.
15. Asati, V.; Bajaj, S.; Mahapatra, D.K.; Bharti, S.K.; *Med Chem Res*. **2016**, *25*, 94.
16. Asati, V.; Bharti, S.K.; Rathore, A.; Mahapatra, D.K.; *Indian J. Pharm Edu Res*., **2017**, *51*, 436.
17. Chhajed, S.S.; Chaskar, S.; Kshirsagar, S.K.; Haldar, AGM; Mahapatra, D.K.; *Comp Biol Chem*., **2017**, *67*, 260.

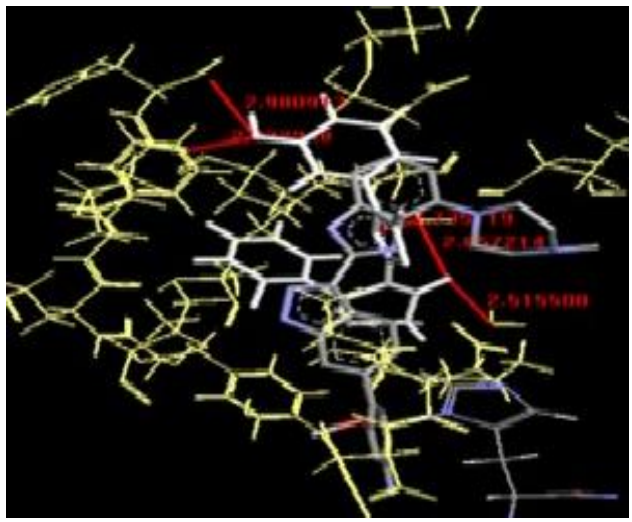
Authors biography

Kanhaiya M. Dadure has taught organic chemistry at various levels. He has also mentored a number of post-graduate and doctorate students in various research projects. His area of interest includes rational designing and synthesis of low molecular weight ligands against druggable targets. Presently, he is serving as reviewer and editorial board member for several journals of international repute. He is a member of a number of professional scientific societies at both national and international levels.

Animeshchandra G. M. Haldar holds 11 years of teaching Organic Chemistry and related Chemical Technology subjects. He has published several research papers, review articles, and book chapters at various reputed levels and presented his original contributions at numerous international/national platforms, for which he received awards from a number of scientific and professional bodies. Presently, he is serving as reviewer for several journals of international repute. He is a member of a number of professional scientific societies.

Debarshi Kar Mahapatra taught medicinal chemistry, organic chemistry, computational chemistry, and chemistry of natural products at various levels and delivered lectures in numerous platforms as resource person. He has also mentored a number of undergraduate and post-graduate students in various research projects. His area of interest includes computer assisted rational designing and synthesis of low molecular weight ligands against druggable targets, natural products research, and development of drug delivery systems.

Graphical Abstract



A8 has been successfully identified as the best compound through the in silico exploration with an impressive Dock Score of -11.0653 Kcal/mol by specifically interacting with the amino acid residues 85-GLN, 85-LEU